PHOSPHORAMIDE CHIRAL CATALYSTS FOR ENVIRONMENTALLY FRIENDLY ASYMMETRIC ORGANOCATALYTIC PROCESSES

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Abstract

Phosphoramides and thiophosphoramides were prepared from optically pure 1,2-diamines and were used as chiral organocatalysts in the asymmetric Michael additions of different Michael-donors to *N*-substituted maleimides. The 1,2-diphenylethane-1,2-diamine derived thiophosphoramide, which could be prepared in good yield in a one-step procedure, was found to be excellent catalyst in the addition of aldehydes to various maleimide derivatives. Products resulted in reactions of ketones with maleimides were also obtained in high yields and enantioselectivities. The thiophosphoramide derivative was efficient in the asymmetric conjugate addition of other carbonyl compounds, such as □-diketones and □-keto esters, as well. Investigations of these reactions led to valuable conclusions as concerns the structural requirements of the catalyst and reactants needed for obtaining high activities and stereoselectivities. Due to the low catalyst amount and the solvent applied, these reactions could be carried out in a more environmentally benign way as with the previously used chiral organocatalysts.

Introduction

Extremely significant economic advantages of asymmetric catalytic processes have led to the explosive development of chiral enantioselective catalysts [1,2]. Most of the widely used catalysts are transition metal complexes, which raises some concerns. For example, the toxicity of transition metals is a significant disadvantage of these methods, as their removal from the final product is challenging for technological processes in most of the cases. In the last few decades, a new field of research has emerged and led to a solution in catalyst development, the so-called organocatalysis. Nowadays, this area is in the forefront of the modern chemical research. Its name also suggests that it uses small organic molecules called “microenzymes” that do not need metals at all in catalytic processes. The most significant results of organocatalysis were in the field of asymmetric reactions. These catalysts are widely applied in C-C coupling reactions, C-N and C-O bond formations, reductions and oxidations.

One of the most important asymmetric C-C coupling reaction is the Michael addition [3-5], a highly efficient method for connecting small molecules to create new chiral centers in a stereospecific step. Asymmetric Michael additions are widely applied for preparing optically pure fine chemicals. Many donors and acceptors can be used, allowing the synthesis of a wide variety of products. Maleimides – as Michael-acceptors – have significant application possibilities in asymmetric organocatalysis. One of the easiest way to prepare enantioenriched succinimide compounds is the direct Michael addition of nucleophiles to maleimides. The presence of succinimide moiety can be seen in natural products and clinical drugs [6], being part of pharmaceuticals used in the treatment of epilepsy [7], depression [8], neurodegenerative disease and HIV [9]. The promising results of previous studies also demonstrate that further research aimed at producing optically pure succinimides and their testing may be important in the future.

In the present work, our aim was to study the applicability of newly synthesized phosphoramide catalysts in various asymmetric Michael additions [10]. We determined the

optimal reaction conditions (temperature, reaction time, amount of solvent and reagent) for each reaction to achieve the best enantioselectivities and conversions.

Experimental

Optically pure 1,2-diamines and the chloro(thio)phosphate derivatives were purchased from Sigma-Aldrich and used as received. Carbonyl compounds, a few *N*-substituted maleimides and the other donors and acceptors were commercial products and were used without purification. Solvents, reagents and additives of analytical grades were used in all reactions. To prepare new maleimides we purchased analytical grade primary amines and maleic anhydride.

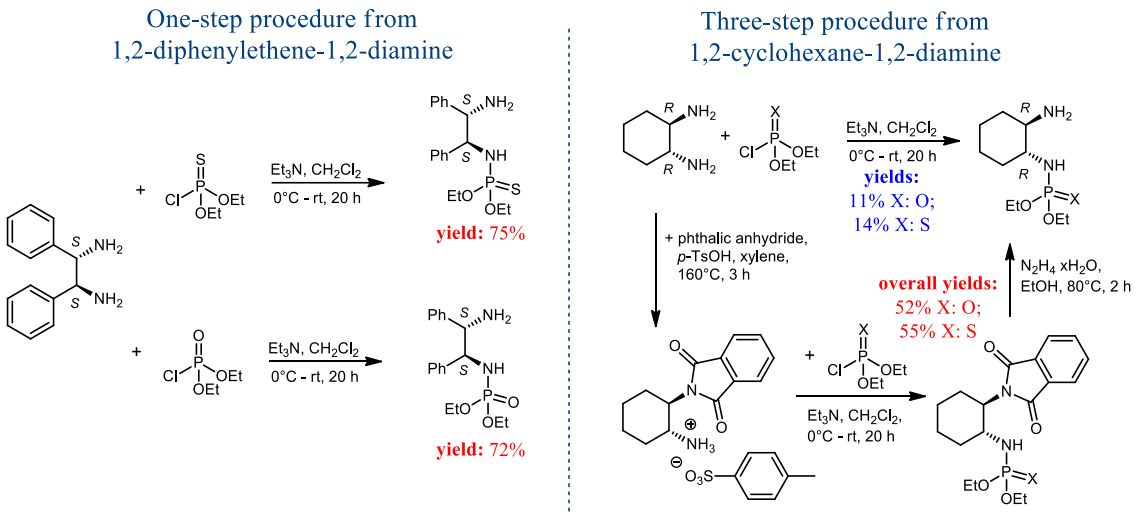
The catalysts were prepared in one or in three-step preparation methods. In the one-step method a solution of 1,2-diphenylethane-1,2-diamine and equivalent amount of Et_3N in dry CH_2Cl_2 was flushed with N_2 and cooled to 0°C. To this solution *O,O'*-diethyl chlorothiophosphate dissolved in dry CH_2Cl_2 was added dropwise in 2 h. Following one day, water was added and the product was extracted in CH_2Cl_2 followed by purification by flash chromatography. In the three-step method first we had to protect one of the amino group of the diamine and after phosphorylation of the free amine in the third step we removed the protecting group to obtain the appropriate catalyst. Maleimides were synthesized from maleic anhydride and the corresponding primary amine using sodium acetate and acetic anhydride in one day at 70°C. The crude products were purified by flash chromatography. Catalytic Michael additions were performed in vials with magnetic stirring. The chiral catalyst was dissolved in the given solvent, followed by the addition of a maleimide derivative and 2-3 equivalents of nucleophile. The mixture was stirred at the indicated temperature. After the given times the products were extracted with ethyl acetate and analyzed.

Products resulted in the Michael additions were analyzed by GC-MSD and GC-FID using chiral capillary columns. Larger scale experiments were also carried out and the resulted products were purified by column chromatography for determination of the isolated yields. The pure compounds were characterized by ^{1}H- and ^{13}C-NMR spectroscopy. For identification of the newly prepared organocatalysts and for mechanistic investigations the ESI-MS spectra were recorded.

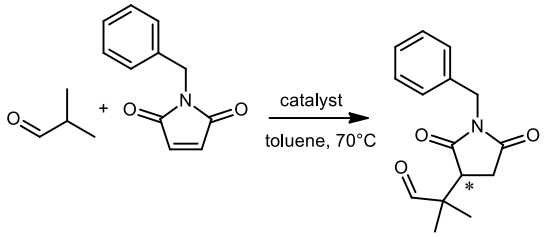
Results and discussion

Initially we have attempted to prepare phosphoramides and thiophosphoramides from optically pure (*R,R*)-1,2-cyclohexanediamine or (*S,S*)-1,2-diphenylethane-1,2-diamine by a one-step procedure using *O,O'*-diethyl(thio)phosphoric chlorides (Scheme 1). This method was successful using 1,2-diphenylethane-1,2-diamines, however, in reactions of 1,2-cyclohexanediamines low yields were obtained. Thus, the three-step procedure was applied to reach satisfactory yields with the latter diamines.

With these optically pure diamine derivatives in hand we started our catalytic studies by testing them as organocatalysts in the asymmetric conjugate addition of isobutyraldehyde to *N*-benzylmaleimide leading to the succinimide derivative shown in Scheme 2. Phosphoramide and thiophosphoramide having cyclohexane backbone were highly active catalysts in the test reaction, assuring complete conversion of the maleimide in one hour at room temperature (rt). Product resulted in good yield and in 94% *ee*'s. The organocatalysts with 1,2-diphenylethane scaffold were less active as compared with the previous catalysts at room temperature in three days. However, high *ee* (>99%) was obtained. Higher conversion, without altering the *ee* value, was reached in one day by increasing the reaction temperature to 70°C.



Scheme 1. Preparation of (thio)phosphoramides from optically pure C2-symmetric 1,2-diamines.

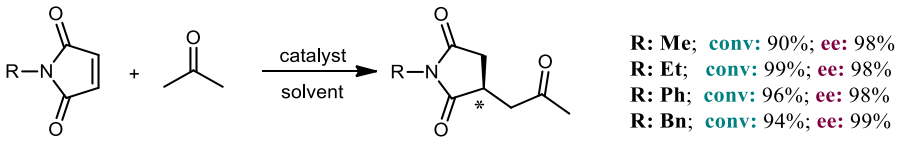


conv: 99%; **ee:** >99%

Scheme 2. The selected test reaction.

Owing to the excellent performance of thiophosphoramide derived from 1,2-diphenylethane-1,2-diamine we have examined the possibility of decreasing the organocatalyst amount. Although, 1.6 mol% was enough to obtain over 60% conversion in one day at 70°C, 2.5 mol% catalyst was necessary for close to complete transformation of the *N*-benzylmaleimide. However, high *ee* value (99%) was obtained even with the lower amount of catalyst.

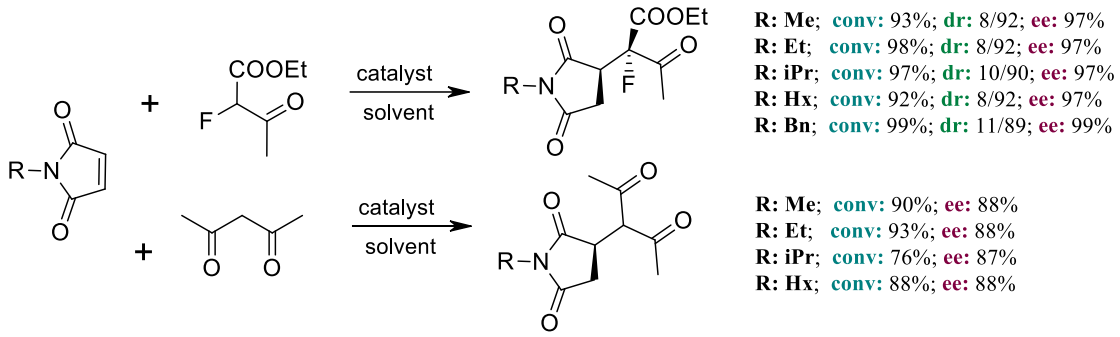
After studying the test reaction, we began to investigate the use of various carbonyl compounds – simple aldehydes and ketones – as Michael donors in reactions with maleimide derivatives. Similar results were obtained with various aldehydes; however, the products resulted in low diastereomeric ratios in case two chiral centers were formed in the reaction. Reaction in which ketones were used as nucleophiles also proceeded excellently, as illustrated by results obtained using acetone under similar conditions as employed in reactions of aldehydes (Scheme 3.). In these reactions, almost complete transformations of various maleimides were reached and the products resulted in high optical purities.



Scheme 3. Michael addition of acetone to maleimide derivatives.

The applicability of the thiophosphoramide derivative was also investigated in other asymmetric conjugate additions, such as those of □-diketones and □-keto esters to maleimides. The conjugate addition of ethyl-2-fluoroacetoacetate and acetylacetone to different *N*-alkyl or

N-benzyl maleimides afforded the corresponding Michael adducts in good yields and excellent enantioselectivities as shown on Scheme 4. With the latter donor, we obtained slightly lower values in each reaction. Contrary to aldehyde nucleophiles, beside high ee values, the reactions of ethyl-2-fluoroacetoacetate also afforded good diastereomeric ratios.



Scheme 4. Michael addition of a □-keto ester and a □-diketone to maleimides.

We also applied the organocatalyst in other Michael additions. Reactions of carbonyl compounds to □-nitrostyrene and that of nitromethane to □,□-unsaturated ketones were also investigated. In each case it was necessary to optimize the reaction conditions. High conversions and *ee* values were reached in these reactions with the (thio)phosphoramide catalysts. Furthermore, high yields were obtained in all reactions, which were carried out in 1 mmol of maleimide derivatives.

Conclusion

Our research aimed at tuning the structure of chiral C_2-symmetric diamines derived bifunctional organocatalysts for application in the asymmetric Michael addition of several Michael acceptors and donors, by using (thio)phosphoramide moieties as hydrogen-bond donor groups. It was found that phosphoramides and especially thiophosphoramides are really efficient in the investigated reactions. Although the thiophosphoramide having cyclohexane backbone gave complete transformations in a much shorter time, the enantioselectivities obtained were lower than those obtained with catalysts bearing diphenylethane backbone. The use of 1,2-diphenylethane-1,2-diamine derived thiophosphoramide, which could be prepared in good yields in a one-step procedure, afforded optically pure products in high yields and also allowed the use of low amount, down to 2.5 mol%, of catalyst. The applicability of the thiophosphoramide derivative was investigated in several asymmetric conjugate additions to various maleimides. With this organocatalyst, high conversions and enantioselectivities can be achieved in these Michael additions, thus provided and environmentally benign procedure of preparing optically pure succinimides needed in the pharmaceutical industry.

Acknowledgements

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